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14. ABSTRACT

This project is a cross-sectional observational study of 391 patients receiving chemotherapy for breast cancer. The purpose of this project was to identify demographic, clinical, and psychological characteristics associated with the severity of pain and co-occurring symptoms (i.e., fatigue, sleep disturbance, depressive symptoms), as well as to identify genetic variations in cytokine genes associated with the experience of these symptoms, Latent class profile analysis was used to identify subgroups of patients with distinct experiences with this symptom cluster (i.e., pain, fatigue, sleep disturbance, depressive symptoms). Three subgroups were identified and differences in demographic and clinical characteristics, psychological symptoms, and quality of life among the subgroups were evaluated. Quality control procedures, genotype scoring, and analyses for ancestry informative markers were conducted, with final statistical analyses for genetic data underway. The identification of factors that contribute to variability in the experience of pain and associated symptoms may help to identify high-risk patients and inform intervention efforts.

15. SUBJECT TERMS

Pain, fatigue, sleep disturbance, depressive symptoms, symptom cluster, breast cancer, gene association, cytokines, inter-individual variability

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Introduction

Pain is a highly prevalent and distressing problem associated with breast cancer and its treatment. In fact, pain occurs in approximately 50% of breast cancer patients. Pain is identified as one of the most upsetting symptoms that patients experience,[1,2] and has deleterious effects on their quality of life (QOL) and functional status. However, significant individual variability exists in the experience of pain. Characteristics that contribute to this inter-individual variability, particularly during active treatment for breast cancer, remain largely unexplored.

Clinical experience suggests that pain rarely occurs as a single symptom, but more often co-occurs with a number of other symptoms. The observation that multiple symptoms often co-occur has contributed to the growing acceptance of a biopsychosocial model of pain and has inspired the concept of a "symptom cluster." Importantly, the inclusion of co-occurring symptoms in an evaluation of cancer pain may provide a more comprehensive and clinically relevant picture of the pain experience as a whole.

Pain related to cancer or its treatment was found to be interrelated with fatigue, sleep disturbance, and depressive symptoms.[3] Of note, these four symptoms are highly prevalent in oncology patients.[4-6] Previous studies of oncology outpatients identified distinct subgroups of patients based on their experience with the symptom cluster of pain, fatigue, sleep disturbance, and depressive symptoms, using cluster analysis or latent class profile analysis (LCPA).[7-11] Common to these studies was the identification of a subgroup of patients who had low severity scores on all four symptoms ("All Low") and a subgroup of patients who had high severity scores on all four symptoms ("All High"). Consistent across the studies, membership in the All High latent class was associated with the lowest functional status and poorest QOL. The observation that very few demographic and clinical characteristics distinguished among the classes suggests that other factors are at play. Differences in psychological and genetic factors may contribute to this variability.

Previous candidate gene studies by our group found that common variations in cytokine genes were associated with the severity of fatigue[12], sleep disturbance[13], and depression[14] and the co-occurrence of these symptoms with pain in patients undergoing radiation therapy and their family caregivers. Importantly, the symptom cluster of interest (i.e., pain, fatigue, sleep disturbance, depression) closely resembles components of cytokine-induced sickness behavior observed in animal models[15,16] and in humans. As such, the cytokine signaling pathway may play an important role in mediating these symptoms.

The identification of factors that contribute to variability in the experience of pain and associated symptoms may provide valuable information that will improve our ability to identify patients at higher risk of more severe symptoms. Such factors may also represent novel targets for pain prevention and management in women with breast cancer.

This project was a cross-sectional observational study of 391 women undergoing active chemotherapy treatment for breast cancer at the University of California, San Francisco (UCSF) Comprehensive Cancer Center, El Camino Hospital, and Alta Bates Summit Medical Center between February, 2010 and November, 2013. The purpose of the project was to identify demographic, clinical, psychological, and genetic factors associated with the severity of pain and co-occurring symptoms in the week following chemotherapy administration (i.e., acute symptoms).

Keywords

Pain, fatigue, sleep disturbance, depressive symptoms, symptom cluster, breast cancer, gene association, cytokines, inter-individual variability

Overall Project Summary

Participant Recruitment, Enrollment, and Data Collection

Participant screening and recruitment continued at the sites as described previously. In brief, at UCSF, where the majority of participants were recruited, we (PI and research nurses) screened pharmacy charts at the Infusion Center daily to identify potentially eligible patients to approach the following day during their appointment times. At El Camino and Alta Bates, weekly schedules were screened for potentially eligible patients based on type of infusion. Nurses or physicians verified participant's suitability before patients were approached to participate in the study.

Patients who were enrolled and had complete data at the time of sample submission to the UCSF Genome Core (timing based on the needs of the parent project) were included in the final sample for phenotypic and genotypic analyses. In total, 500 patients were enrolled. Of these participants, 109 (21.8%) withdrew from the study after enrollment. Complete data (blood specimen and questionnaire data) were available for 391 breast cancer patients. On average, participants were 53.6 years of age (standard deviation = 11.1; range: 21 – 89). For details regarding ethnicity and race, see Table 1 below.

Table 1. Breakdown of total sample by ethnic and racial group.

Ethnic category	Number (%) of subjects enrolled
Hispanic or Latino	20 (5.1)
Not Hispanic or Latino	355 (90.8)
Unreported	17 (4.3)
TOTAL:	**391 (100.0)**
Racial category	**Number (%) of subjects enrolled**
White	254 (65.0)
Asian	56 (14.3)
Black or African American	27 (6.0)
Mixed Ethnic Background/Native American/Pacific Islander/Other	39 (10.0)
Unreported	15 (3.8)
TOTAL:	**391 (100.0)**

As mentioned above, this sample size includes those participants who gave blood for genomic analysis and who completed demographic questionnaires, as well pain, fatigue, sleep disturbance, and depressive symptom inventories. Screening and data collection were tracked through a secure study log, maintained by our research coordinator, Ann Murai, and project director, Judy Mastick. Data were scanned, cleaned, and exported periodically to a statistical software package (i.e., SPSS), using Optical Mark Recognition (OMR) technology by research assistants. Our research team met regularly to discuss progress with regards to recruitment, enrollment, and data collection.

Training in Genetics

Over the duration of my fellowship, I attended several Human Population Genetics Workshops led by my co-mentor, Dr. Bradley Aouizerat, and bioinformaticist, Dr. Kord Kober. Through this series, I was exposed to diverse topics from basic concepts related to population genetics that included hands-on training in genotype scoring, cleaning, and haplotype construction to cutting-edge gene expression techniques that are ongoing in Dr. Aouizerat's laboratory. As a result, I was afforded the opportunity to be co-author on a manuscript that involved gene expression profiling of evening fatigue in 44 breast cancer patients undergoing chemotherapy, which was recently submitted to *BMC Medical Genomics.*

I continued to meet with my co-mentor, Dr. Aouizerat, throughout my fellowship. In large part, these meetings were related to the hands-on analysis and interpretation of genetic data for two first-author manuscripts that I prepared related to the association between potassium channel gene variations and breast pain in women with breast cancer. The first paper, related to the occurrence of preoperative breast pain, was published this year in the *Journal of Neurogenetics*. The second paper, related to persistent postoperative breast pain was recently accepted in *Pain*. See "Publications" below.

In year 2, I undertook the Advanced Training in Clinical Research (ATCR) Certificate Program offered by UCSF's Department of Epidemiology and Biostatistics. As a result, I received formal training in "Molecular and Genetic Epidemiology" and "Statistical Methods in Genetic Epidemiology", which covered basic fundamental issues, as well as specific approaches to the design and interpretation of genetic studies. In particular, I gained an understanding of various molecular and genetic techniques, approaches to linkage and association studies, gene x environment interactions, population substructure, quality control procedures, and ethics in genetic research. I was able to directly apply skills I acquired in these courses in order to better evaluate, interpret, and disseminate our own genetic findings more effectively.

Custom Genotyping Array

As outlined previously, due to the timeline of the parent project and the benefit of economy of scale, a larger number of SNPs across a greater number of cytokine genes were evaluated than initially proposed (See Table 2 below for genes evaluated).

DNA samples were submitted and processed by the UCSF Genome Core Facility in Year 2. In Year 3, data were received from the Genome Core and quality control procedures, genotype scoring, and analyses for ancestry informative markers (AIMS; SNPs known to vary by ethnicity) were completed to prepare the data for statistical analyses. In addition, genotype data for the candidate cytokine genes for the proposed study were extracted from the parent project sample. The funds budgeted for genotyping in Years 1 through 3 contributed to the custom array.

Table 2. List of cytokine genes evaluated for the current study

Cytokine Genes		Cytokine "Receptor" Genes				
IFNG1	IL17B	IFNGR1	CXCR2	EDA2R	TNFRSF13C	TRAF1
IFNG2	IL17C	IFNGR2	IL10RA	FAS	TNFRSF14	TRAF2
IL1	IL17D	IL1R1	IL10RB	LTBR	TNFRSF18	TRAF3
IL1A	IL17F	IL1R2	IL13RA1	NGFR	TNFRSF19	TRAF4
IL1B	NFKB1	IL1RN	IL13RA2	PSMD2	TNFRSF1A	TRAF5
IL2	NFKB2	IL1RAP	IL17RA	RELT	TNFRSF1B	TRAF6
IL4	TNFA	IL2RA	IL17RB	TNFRSF10A	TNFRSF21	TRAP1
IL6		IL2RB	IL17RC	TNFRSF10B	TNFRSF25	
IL8		IL2RG	IL17RD	TNFRSF10D	TNFRSF4	
IL10		IL4R	NKRF	TNFRSF11A	TNFRSF6B	
IL13		IL6R	CD27	TNFRSF11B	TNFRSF8	
IL17A		CXCR1	CD40	TNFRSF12A	TNFRSF9	

Statistical analyses for genetic data are in process and will be completed shortly. Due to the rich phenotypic data collected from this study, we decided to prepare two manuscripts based on the study's findings. The initial manuscript describes the identification of subgroups of patients with distinct symptom experiences and determines differences in demographic and clinical characteristics, psychological symptoms, pain characteristics, and quality of life (QOL) among the subgroups. This manuscript is currently under review by our research team members and will be submitted to a peer-reviewed journal before the end of the year. The second manuscript will extend these results with the genetic analyses. In this paper, we will identify and discuss variations in cytokine genes that differ with respect to subgroup membership.

Latent Class Profile Analysis: Clustering Patients

In Year 3, we completed our latent class profile analysis (LCPA) to identify subgroups (i.e., latent classes) of patients who reported similar experiences with the symptom cluster of pain, fatigue, sleep disturbance, and depressive symptoms. Based on these criteria, a 3-class solution fit the model best. See Table 3 for latent class solutions and their fit indices.

Table 3. Latent Class Solutions and Fit Indices for 2-Class Through 4-Class Solutions

Model	LL	AIC	BIC	VLMR	Entropy
2 Class	-2760.58	5563.16	5646.50	88.22***	.84
3 Class[a]	-2743.73	5541.46	5648.61	33.70*	.76
4 Class	-2732.91	5531.81	5662.78	21.66	.74

* p < .05; ** p < .01; *** p < .001.[a] The three class solution was selected because the AIC for that solution was lower than the AIC for the 2-class solution and the VLMR suggested that the 3-class model fit the data better than the 2-class model. Note the VLMR for the 4-class solution indicated that the 4-class solution was not significantly better than the 3-class solution.

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; LL = log-likelihood; VLMR = Vuong-Lo-Mendell-Rubin likelihood ratio test.

As shown in Table 4, 140 patients (35.8%) were classified in the "Low" latent class, 189 patients (48.3%) were classified in the "Moderate" latent class, and 62 patients (15.9%) were classified in the "All High" latent class. The latent classes were named based on mean severity scores for pain, depressive symptoms, sleep disturbance, and evening fatigue. To facilitate the naming of the subgroups, scores for each of the latent classes were compared to established cut-points in the literature, and to each other. Based on established cut-points for worst pain severity in oncology patients (i.e., mild pain = 1-4; moderate pain = >4-7; severe pain = >7-10),[17] patients in the Low class reported mild worst pain scores (mean = 2.3), patients in the Moderate class reported moderate worst pain scores (mean = 6.9), and patients in the All High class reported severe worst pain scores (mean = 7.2). Depressive symptom scores were under the clinically meaningful cut-point of 16 for patients in the Low and Moderate classes. In contrast, the mean CES-D score for the All High class well-exceeded this cut-point. General sleep disturbance scale scores indicated that all patients, regardless of latent class membership were "poor sleepers." However, sleep disturbance scores differed significantly among the three latent classes (i.e., Low < Moderate < All High). In terms of evening fatigue, patients in the Moderate and All High classes reported high levels of evening fatigue compared to patients in the Low class.

Table 4. Differences in Symptom Severity Scores Among the Latent Classes

Symptom	Low (1) n=140 (35.8%)	Moderate n=189 (48.3%)	All High n=62 (15.9%)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
Worst pain intensity score (*pain*)	2.3 (1.3)	6.9 (1.6)	7.2 (1.9)	F=113.36, p<.001 1<2 and 3
CES-D total score (*depressive symptoms*)	9.8 (7.2)	11.7 (6.7)	33.7 (7.1)	F=269.43, p<.001 1 and 2<3
GSDS total score (*sleep disturbance*)	48.7 (20.4)	55.7 (18.9)	69.3 (19.3)	F=22.87, p<.001 1<2<3
Evening fatigue score (*fatigue*)	5.4 (2.0)	6.1 (1.8)	6.5 (1.9)	F=7.78, p<.001 1<2 and 3

Abbreviations: CES-D = Center for Epidemiological Studies – Depression Scale, GSDS= General Sleep Disturbance Scale, SD = standard deviation

Descriptive statistics and frequency distributions were calculated for patients' demographic and clinical characteristics, psychological symptoms (i.e., state and trait anxiety, cognitive function), pain characteristics (e.g., pain interference, pain qualities), and QOL scores. Data were analyzed using SPSS v.21.0 (IBM, Armonk, NY). One-way analyses of variance, Kruskal-Wallis, or Chi-square tests with Bonferroni corrected post hoc comparisons were performed to evaluate for differences among the latent classes.

Table 5 displays only those demographic and clinical characteristics that differed significantly among the subgroups. Between-group differences in the expected direction were found for functional status, comorbidities, and symptom burden. Patients in the All High class were less likely to be married or partnered and had a lower annual household income than patients in the Low and Moderate classes. Patients in the Moderate class were less likely to be employed than patients in the Low class.

Table 5. Differences in demographic and clinical characteristics among the latent classes

Demographic Characteristics	Low (1) n=140 (35.8%)	Moderate n=189 (48.3%)	All High n=62 (15.9%)	Statistics
	% (n)	% (n)	% (n)	
Married or partnered (% yes)	75.8 (100)	69.3 (122)	46.7 (28)	X^2=16.3, p<.001 1 and 2>3
Currently employed (% yes)	54.5 (72)	33.3 (59)	36.7 (22)	X^2=14.70, p=.001 1>2
Annual household income				
Less than $30,000	6.3 (7)	14.0 (22)	29.8 (17)	KW=16.53, p<.0001 1 and 2>3
$30,000 to $70,000	18.0 (20)	20.4 (32)	15.8 (9)	
$70,000 to $100,000	14.4 (16)	17.2 (27)	22.8 (13)	
Greater than $100,000	61.3 (68)	48.4 (76)	31.6 (18)	

Clinical Characteristics	Mean (SD)	Mean (SD)	Mean (SD)	Statistics
KPS Score (*functional status*)	85.0 (10.1)	80.2 (10.9)	72.5 (13.9)	F=24.53, p<.0001 1>2>3
SCQ score (*comorbidities*)	4.6 (2.5)	6.4 (3.8)	7.8 (4.4)	F=19.47, p<.0001 1<2<3
Mean number of MSAS symptoms (*symptom burden*)	11.2 (5.7)	14.9 (6.1)	20.5 (7.8)	F=44.64, p<.0001 1<2<3

Figure 1 displays the patients' scores for the Spielberger's State-Trait Anxiety Inventory (STAI-S and STAI-T) and for the Attentional Function Index (AFI; evaluates perceived cognitive functioning). Significant between-group differences for all of these instruments were found in the expected direction (Low < Moderate < All High for anxiety; Low > Moderate > High for attentional function; all $p < 0.05$).

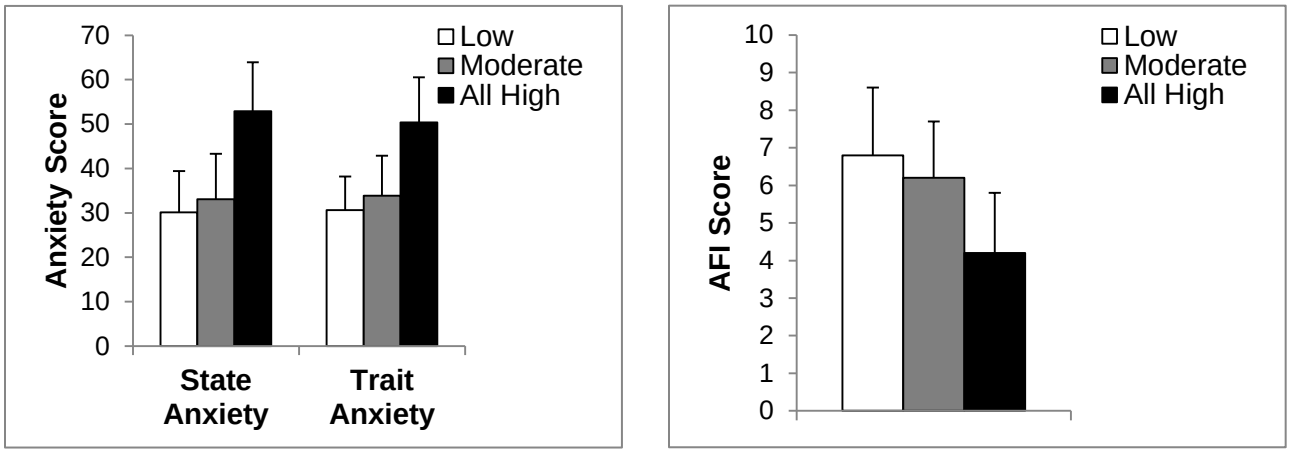

Figure 1. Psychological symptom scores by latent class.

As shown in Table 6, several pain characteristics differed significantly among the latent classes. Compared to the Low class, patients in the Moderate and All High classes reported significantly higher average and worst pain ratings, a higher number of days that pain interfered with mood and/or activities, a higher number of pain sites, and lower satisfaction with pain treatment.

Table 6. Differences in pain characteristics among the latent classes

Characteristic	Low (1) n=140 (35.8%)	Moderate n=189 (48.3%)	All High n=62 (15.9%)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
Worst pain intensity	2.3 (1.3)	6.9 (1.6)	7.2 (1.9)	F=113.36, p<.001 1<2 and 3
Average pain intensity	1.4 (1.3)	3.9 (1.9)	4.2 (1.8)	F=26.34, p<.001 1<2 and 3

Number of days pain interferes with mood and/or activities	1.4 (2.1)	3.2 (2.4)	3.8 (2.4)	F=10.84, p<.001 1<2 and 3
Overall satisfaction with pain treatment	8.2 (2.6)	6.7 (2.8)	5.8 (3.0)	F=5.42, p=.005 1>2 and 3
Pain interference score	1.2 (1.7)	3.6 (2.4)	5.1 (2.4)	F=28.63, p <.001 1<2<3
	% (n)	**% (n)**	**% (n)**	**% (n)**
Occurrence of pain (% yes)	24.8 (32)	100.0 (178)	84.7 (50)	X^2=211.97, p<.001 1<3<2
Source of pain No pain Related to cancer or treatment NOT related to cancer or treatment BOTH cancer and non-cancer related Pain	 75.8 (97) 7.0 (9) 9.4 (12) 7.8 (10)	 0.0 (0) 44.3 (78) 23.9 (42) 31.8 (56)	 15.3 (9) 35.6 (21) 8.5 (5) 40.7 (24)	X^2=222.46, p<.001 1>3>2 1<2 and 3 1<2 1<2 and 3
Total number of pain sites	5.3 (3.8)	9.7 (8.8)	12.7 (10.9)	F=7.28, p=.001 1<2 and 3
Pain qualities (% yes) Aching	 54.5 (18)	 81.3 (135)	 83.0 (39)	 X^2=12.35, p=.002 1<2 and 3
Throbbing	28.1 (9)	40.5 (66)	55.3 (26)	X^2=6.11, p=.047 no sig pw comp
Stabbing	12.1 (4)	27.9 (46)	47.8 (22)	X^2=12.43, p=.002 1 and 2<3
Gnawing	3.1 (1)	27.3 (45)	32.6 (15)	X^2=10.01, p=.007 1<2 and 3
Exhausting	15.2 (5)	36.1 (60)	53.2 (25)	X^2=12.14, p=.002 1<3
Miserable	3.1 (1)	27.7 (46)	55.3 (26)	X^2=25.86, p<.001 1<2<3
Unbearable	6.3 (2)	7.8 (13)	21.3 (10)	X^2=7.86, p=.020 2<3

The prevalence of pain in the total sample was striking. Across the classes, nearly two-thirds of the patients reported experiencing pain in the week following CTX administration. In fact, 100% of the Moderate class reported pain scores that were just below the cut-points for moderate average pain and severe worst pain.[17] While a smaller percentage of patients in the All High class (85%) reported pain, this group of patients reported moderate average and severe worst pain intensity scores. However, it is interesting to note the differences in pain characteristics between these two classes. For example, despite similar pain severity, patients in the All High class reported greater interference of pain with mood and daily activities than patients in the Moderate class. Moreover, a higher proportion of patients in the All High class described pain using qualities that reflect the affective dimension of the pain experience (e.g., exhausting, miserable, unbearable).

Finally, Table 7 displays subscale and total QOL scores among the latent classes. With the exception of the spiritual well-being subscale, significant differences were found among all

three classes in the expected direction (i.e., All High < Moderate < Low). For the spiritual well-being, compared to patients in the Moderate class, patients in the All High class had significantly lower scores.

Table 7. Differences in quality of life scores among the latent classes

Quality of Life Scores	Low (1) n=140 (35.8%)	Moderate n=189 (48.3%)	All High n=62 (15.9%)	Statistics
	Mean (SD)	Mean (SD)	Mean (SD)	
QOL total score	6.5 (1.3)	5.9 (1.3)	3.9 (1.0)	F=87.67, p<.001 1>2>3
Physical well-being	7.5 (1.5)	6.4 (1.7)	4.7 (1.4)	F=67.13, p<.001 1>2>3
Psychological well-being	6.2 (1.7)	5.7 (1.7)	3.1 (1.3)	F=74.25, p<.001 1>2>3
Social well-being	6.6 (1.7)	5.7 (1.9)	3.6 (1.5)	F=59.25, p<.001 1>2>3
Spiritual well-being	5.9 (2.0)	6.2 (2.0)	5.2 (2.1)	F=5.35, p=.005 2>3

Abbreviations: QOL = quality of life, SD = standard deviation

The finding that QOL differed significantly among all of the latent classes was expected. However, the scores reported, particularly by the All High class (e.g., 3.9 out of 10 for overall QOL), are extremely low. Large effect sizes were found for the differences in overall QOL scores between patients in the All High and both the Moderate (d = 1.7) and Low (d = 2.2) classes, which suggest a clinically meaningful reduction in QOL. A moderate effect size was found for the difference between the Low and Moderate classes (d = 0.5). These findings highlight the need for interventions that effectively reduce the severity of these symptoms and associated decrements in QOL.

Other Relevant Training

One-on-one meetings with mentor: Throughout my fellowship, I met regularly with my co-mentor, Dr. Miaskowski, to discuss ongoing analyses, manuscript preparation, career plans, and progress of the proposed research. These meetings have been invaluable to me and my progress and achievements as a postdoctoral fellow. As a result of these meetings, in addition to the two aforementioned genetics papers, I prepared two first-authored companion papers that describe changes over time in pain qualities, pain interference, grip strength, shoulder mobility, and sensations in the breast scar area or axilla among distinct subgroups of women with persistent breast (paper 1) and arm (paper 2) pain following breast cancer surgery. These manuscripts were accepted in *The Journal of Pain* in Year 3 (see "Publications"). Recently, we resubmitted another first-authored paper that describes the persistent breast pain experience of women with and without preoperative breast pain to the *Journal of Pain and Symptom Management*. These findings will provide a basis for a grant submission to better characterize preoperative breast pain. In addition, we will submit the manuscript related to the LCPA analysis described above in the very near future.

One-on-one meetings with biostatisticians: As needed, I met with biostatisticians, Drs. Steven Paul and Bruce Cooper, in order to ensure appropriate statistical analyses and to gain expertise in new statistical methods. As a result of my meetings with Dr. Paul, I was able to independently conduct mixed effects linear modeling to determine how symptoms, quality of life, and muscle strength and mobility changed over time in women with and without preoperative breast pain (I will complete and submit this manuscript in Year 3). Finally, with the assistance of Dr. Cooper, I learned (and continue to learn) how to use the software (Mplus) to run LCPA and other modeling techniques (such as structural equation modeling).

Oncology Symptom Management Research Group (OSMRG) Meetings: Our OSMRG met biweekly to discuss the progress of ongoing analyses and manuscript preparation. These meetings allowed me to work collaboratively with a prolific transdisciplinary team of researchers, who are interested in the phenotypic and genetic determinants of cancer-related symptoms. As a result, I served as co-author on several manuscripts published throughout my fellowship (See "Publications" for co-authored manuscripts published in Year 3).

Reviewer for Scientific Journals

Throughout my fellowship, I served as an ad hoc reviewer for several peer-reviewed journals, including: *Pain; Psycho-Oncology; Journal of Pain*; *General Hospital Psychiatry*; *Pharmacology, Biochemistry, and Behavior*; *Social Neuroscience*; and *Behavioural Processes*. As a result of one of my reviews, I was invited to co-author a "Bridging the Gap" commentary in *Pain* with psychologist and prolific researcher, Amanda C de C Williams. This commentary was published in Year 3 (See "Publications – Invited Articles"). Being a part of the peer review process was invaluable training that I will undoubtedly use throughout my career.

Advanced Training in Clinical Research Certificate (ATCR) Program: As budgeted, in Year 2, I completed the ATCR Certificate Program offered by the Department of Epidemiology and Biostatistics at UCSF. This four-quarter program (August 2012 – May 2013) involved intensive training in methodological, clinical, molecular/genetic epidemiology, database management, as well as a series of courses in biostatistics. These courses were very relevant to my research pursuits and the intensity of the courses allowed me to truly develop and strengthen my skills in these areas. In addition to these didactic courses, I participated in a bi-weekly seminar series that involved the presentation and peer-review of proposals, posters, and manuscripts in progress. This experience allowed me to share my work in a constructive and supportive environment.

Patient Interaction

Perhaps the most valuable part of my training was what I learned from interacting with oncology patients. I was able to observe and appreciate first-hand the tremendous inter-individual variability in the experience of symptoms. Conversations with patients provided relevant perspectives that shaped my interpretation of study findings. In addition to

improving and enriching my current research endeavors, these interactions taught me about compassion and sensitivity. Moreover, I have a newfound genuine appreciation for the vital role of the "research participant."

Key Research Accomplishments

- Compiled and ran descriptive analyses of demographic, clinical, and symptom inventory for data for 391 patients
- Used latent class profile analysis (LCPA) to cluster patients according to severity of pain, fatigue, sleep disturbance, and depressive symptoms
- Completed scoring, cleaning, and extraction of genetic data from custom genotyping array from UCSF Genome Core Facility. Currently, I am completing scoring and cleaning of genetic data for statistical analyses
- Prepared first paper directly related to project goal, "Identification and Characterization of Subgroups of Patients with Distinct Experiences of Pain and Co-occurring Symptoms Following Chemotherapy Administration for Breast Cancer"
- Published first-author paper in *Journal of Neurogenetics*, entitled "Variations in Potassium Channel Genes Are Associated with Breast Pain in Women Prior to Breast Cancer Surgery" as first author (see "Publications" below)
    - Identified 7 single nucleotide polymorphisms and 1 haplotype across 4 potassium channel genes that were associated with occurrence of preoperative breast pain
- Two first-authored companion papers prepared, submitted and accepted in the *Journal of Pain*, titled ""Persistent Breast Pain Following Breast Cancer Surgery is Associated with Persistent Sensory Changes, Pain Interference, and Functional Impairments" and "Persistent Arm Pain is Distinct from Persistent Breast Pain Following Breast Cancer Surgery" (see "Publications" below)
    - Used mixed linear effects modeling to evaluate changes in pain qualities, pain interference, grip strength, shoulder mobility, and sensations in breast scar area and in shoulder/upper inner arm/axilla over time in a sample of women with persistent breast or arm pain following breast cancer surgery
    - See appendices
- First-author manuscript accepted in *Pain*, entitled "Variations in Potassium Channel Genes are Associated with Distinct Trajectories of Persistent Breast Pain Following Breast Cancer Surgery" (see "Publications" below)
    - Identified 7 single nucleotide polymorphisms across 5 potassium channel genes that were associated with persistent postoperative pain
- Presented poster describing longitudinal changes in function, sensation, symptoms, and quality of life following breast cancer surgery in patients with and without preoperative breast pain at the American Pain Society 33nd Annual Scientific Meeting in Tampa, FL (May, 2014; see "Published Abstracts" below)
    - This first-author manuscript was recently re-submitted to *Journal of Pain and Symptom Management* (see "Publications" below)
- Prepared poster titled "Cumulative Life Stress is Associated with Depressive Symptoms in Oncology Outpatients Undergoing Chemotherapy" for the 11th American Psychosocial

Oncology Society Meeting in Tampa, FL (February, 2014; see “Published Abstracts” below)
    - Poster received a “Best Research” award

Conclusion

- Participant recruitment/enrollment exceeded expectations. A total of 391 patients contributed phenotypic and genotypic data for analyses

- Using LCPA, subgroups of women with distinct experiences with pain and co-occurring symptoms (i.e., fatigue, sleep disturbance, depressive symptoms) differed with respect to psychological and pain characteristics; those individuals with the most severe symptom experiences (~16% of the sample) represent a high risk group who experience statistically significant and clinically meaningful reductions in functional status and quality of life

- Common variations in potassium channel genes are associated with both preoperative and persistent post-surgical breast pain. Potassium channels may be intriguing novel targets for pain management

- Long-term clinical surveillance of persistent breast and arm/shoulder pain following breast cancer is necessary as pain is associated with functional impairments and interference with activities of daily living

- Sustained sensory changes (i.e., loss) at surgical scar sites are common among women following surgery for breast cancer. Further investigation of these sensory changes is warranted

- Preoperative breast pain predicts persistent postsurgical breast pain, functional disability, and reduced quality of life. Currently a grant application is in preparation to better characterize preoperative breast pain

Publications, Abstracts, and Presentations

Peer-Reviewed Scientific Journals

Selected Peer-Reviewed Manuscripts Published in Year 03:

1. **Langford DJ**, West C, Elboim C, Cooper BA, Abrams G, Paul SM, Schmidt BL, Levine JD, Merriman JD, Dhruva A, Neuhaus J, Leutwyler H, Baggott C, Ward Sullivan C, Aouizerat BE, Miaskowski C. Variations in potassium channel genes are associated with breast pain in women prior to breast cancer surgery. *Journal of Neurogenetics,* 2014. 28: 122 – 135. (PMID: 24392765)

2. Miaskowski C, Cataldo JK, Baggott CR, West C, Dunn LB, Dhruva A, Merriman JD, **Langford DJ**, Kober KM, Paul SM, Cooper BA, Aouizerat BE. Cytokine gene variations

associated with trait and state anxiety in oncology patients and their family caregivers. *Supportive Care Cancer*, 2014. *In press*. (PMID: 25249351)

3. Miaskowski C, Cooper BA, Melisko M, Chen LM, Mastick J, West C, Paul SM, Dunn LB, Schmidt BL, Hammer M, Cartwright F, Wright F, **Langford DJ**, Lee K, Aouizerat BE. Disease and treatment characteristics do not predict symptom occurrence profiles in oncology outpatients receiving chemotherapy. *Cancer*, 2014. 120: 2371-2378. (PMID: 24797450)

4. Saad S, Dunn LB, Koetters T, Dhruva A, **Langford DJ**, Merriman JD, West C, Paul SM, Cooper B, Cataldo J, Hamolsky D, Elboim C, Aouizerat BE, Miaskowski C. Cytokine gene variations associated with subsyndromal depressive symptoms in patients with breast cancer. *European Journal of Oncoloy Nursing*, 2014. 18: 397-404. (PMID: 24726621)

5. Miaskowski C, Paul SM, Cooper B, West C, Levine JD, Elboim C, Hamolsky D, Abrams G, Luce J, Dhruva A, **Langford DJ**, Merriman JD, Kober K, Baggott C, Leutwyler H, Aouizerat BE. Identification of patient subgroups and risk factors for persistent arm/shoulder pain following breast cancer surgery. *European Journal of Oncology Nursing*, 2014. 18: 242-253. (PMID: 24485012)

6. Stephens K, Cooper BA, West C, Paul SM, Baggott CR, Merriman JD, Dhruva A, Kober KM, **Langford DJ**, Leutwyler H, Luce JA, Schmidt BL, Abrams GM, Elboim C, Hamolsky D, Levine JD, Miaskowski C, Aouizerat BE. Associations between cytokine gene variations and severe persistent breast pain in women following breast cancer surgery. *Journal of Pain*, 2014. 15: 169-180. (PMID: 24411993)

7. Alfaro E, Dhruva A, **Langford DJ**, Koetters T, Merriman JD, West C, Dunn LB, Paul SM, Cooper B, Cataldo J, Hamolsky D, Elboim C, Kober K, Aouizerat BE, Miaskowski C. Associations between cytokine gene variations and self-reported sleep disturbance in women following breast cancer surgery. *European Journal of Oncology Nursing*, 2014. 18: 85-93. (PMID: 24012192)

8. Merriman JD, Aouizerat BE, **Langford DJ**, Cooper BA, Baggott CR, Cataldo JK, Dhruva A, Dunn L, West C, Paul SM, Ritchie CS, Swift PS, Miaskowski C. Preliminary evidence of an association between an interleukin 6 promoter polymorphism and self-reported attentional function in oncology patients and their family caregivers. *Biological Research in Nursing*, 2014. 16:152-159.

Peer-Reviewed Publications Accepted/In Press in Year 03:

1. **Langford DJ**, Paul SM, West CM, Dunn LB, Levine JD, Kober KM, Dodd MJ, Miaskowski C, Aouizerat BE. Variations in potassium channel genes are associated with

distinct trajectories of persistent breast pain following breast cancer surgery. *Accepted in PAIN,* November 19, 2014.

2. **Langford DJ**, Paul SM, West C, Levine JD, Hamolsky D, Elboim C, Schmidt BL, Cooper BA, Abrams G, Aouizerat BE, Miaskowski C. Persistent breast pain following breast cancer surgery is associated with persistent sensory changes, pain interference, and functional impairments. *Accepted in Journal of Pain,* August 20, 2014.

3. **Langford DJ**, Paul SM, West C, Abrams G, Elboim C, Levine JD, Hamolsky D, Luce JA, Kober KM, Neuhaus JM, Cooper BA, Aouizerat BE, Miaskowski C. Persistent arm pain is distinct from persistent breast pain following breast cancer surgery. *Accepted in Journal of Pain,* August 20, 2014.

Peer-Reviewed Publications Revised and Resubmitted in Year 03:

1. **Langford DJ**, Schmidt B, Levine JD, Abrams G, Elboim C, Esserman L, Hamolsky D, Mastick J, Paul SM, Cooper B, Dodd M, Dunn L, Aouizerat B, Miaskowski C. Preoperative breast pain predicts persistent breast pain and disability following breast cancer surgery. *Revised and resubmitted to Journal of Pain and Symptom Management*, October, 2014.

Manuscripts in Preparation for Submission/Submitted to Peer-Reviewed Journals:

1. **Langford DJ**, Cooper BA, Mastick J, Keagy C, Gold MG, Abrams G, Paul SM, Schmidt BL, Aouizerat BE, Miaskowski C. Identification of distinct subgroups of patients based on their experience with pain and associated symptoms during chemotherapy.

2. Kober KM, Dunn LB, Mastick J, Cooper BA, **Langford DJ**, Melisko M, Venook A, Chen LM, Schmidt BL, Levine JD, Miaskowski C, Aouizerat BE. Gene expression profiling of evening fatigue in women undergoing chemotherapy for breast cancer. Submitted to *BMC Medical Genomics*.

Invited Articles

1. **Langford DJ**, de C Williams AC.* The caring, sharing rat? *Pain,* 2014. 155: 1183-1184.** (PMID: 24708992) **equal contribution **invited "Bridging the Gap" commentary*

Published Abstracts

1. **Langford DJ**, Paul SM, Cooper BA, Kober KM, Miaskowsku C, Aouizerat BE. Women with preoperative and persistent breast pain following breast cancer surgery experience enduring psychological and physical symptoms and decreased quality of life. *The Journal of Pain*, 2014. 15: S28.*

2. **Langford DJ**, Dunn LB, Moss DB, Dhruva A, Paul SM, Aouizerat BE, Miaskowski C. Cumulative life stress is associated with depressive symptoms in oncology outpatients undergoing chemotherapy. *Psycho-Oncology*, 2014: 23 (Suppl. 1): 1-144. *Recipient of Best Research Poster Award.

Reportable Outcomes

See “Conclusion” above.

Other Achievements

As a result of my DoD BCRP Postdoctoral Fellowship in addition to my research endeavors, I was able to complete the Advanced Training in Clinical Research (ATCR) certificate program offered by UCSF’s Department of Epidemiology and Biostatistics. In addition, I received two poster awards – Best Genetics Poster by the Genetics Special Interest Group of the American Pain Society and Best Research Poster by the American Psychosocial Oncology Society. Finally, I had the opportunity to present my work at regional and national meetings.

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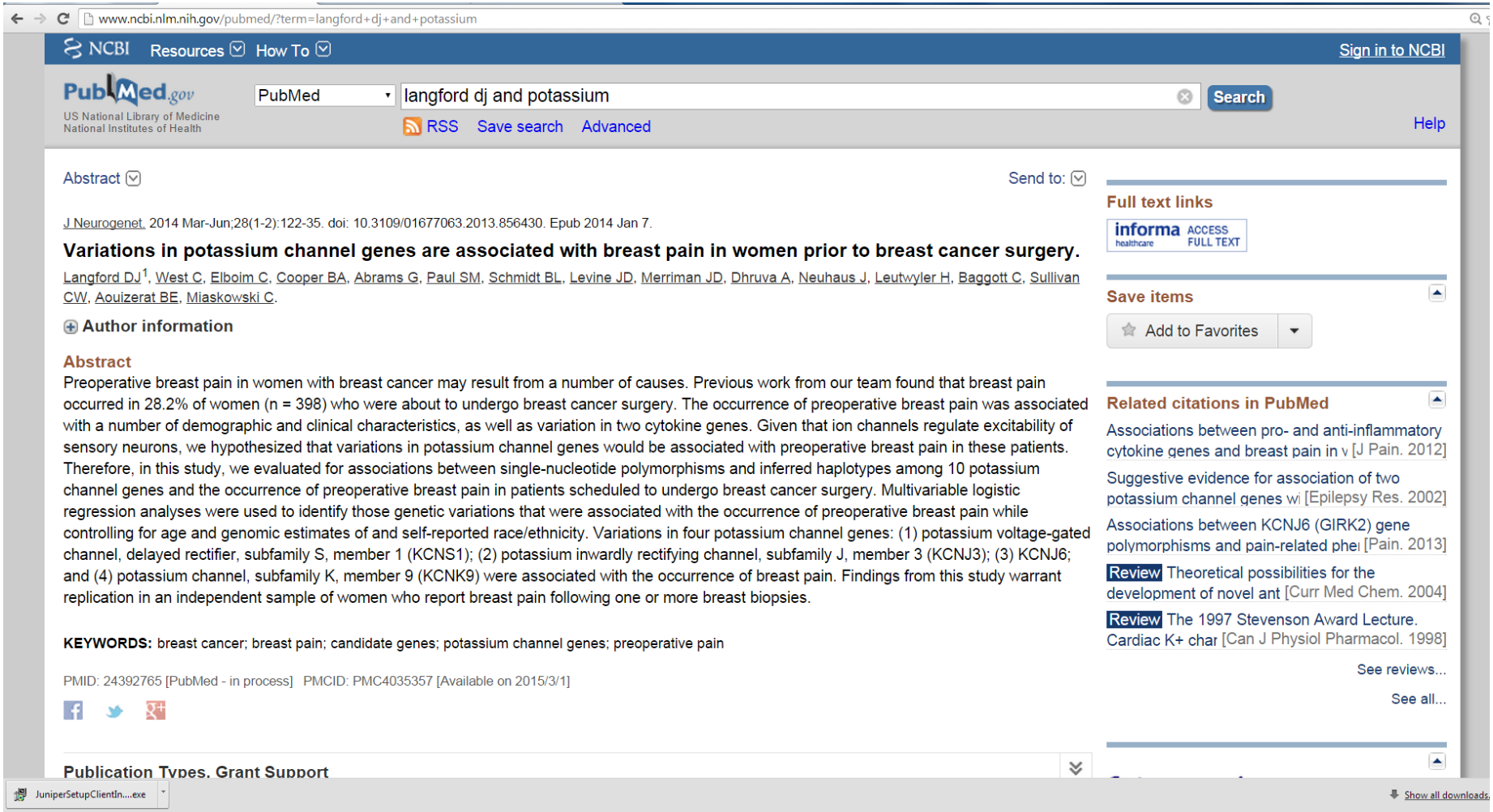
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J Neurogenet. 2014 Mar-Jun;28(1-2):122-35. doi: 10.3109/01677063.2013.856430. Epub 2014 Jan 7.
Variations in potassium channel genes are associated with breast pain in women prior to breast cancer surgery.
Langford DJ[1], West C, Elboim C, Cooper BA, Abrams G, Paul SM, Schmidt BL, Levine JD, Merriman JD, Dhruva A, Neuhaus J, Leutwyler H, Baggott C, Sullivan CW, Aouizerat BE, Miaskowski C.
Author information
Abstract
Preoperative breast pain in women with breast cancer may result from a number of causes. Previous work from our team found that breast pain occurred in 28.2% of women (n = 398) who were about to undergo breast cancer surgery. The occurrence of preoperative breast pain was associated with a number of demographic and clinical characteristics, as well as variation in two cytokine genes. Given that ion channels regulate excitability of sensory neurons, we hypothesized that variations in potassium channel genes would be associated with preoperative breast pain in these patients. Therefore, in this study, we evaluated for associations between single-nucleotide polymorphisms and inferred haplotypes among 10 potassium channel genes and the occurrence of preoperative breast pain in patients scheduled to undergo breast cancer surgery. Multivariable logistic regression analyses were used to identify those genetic variations that were associated with the occurrence of preoperative breast pain while controlling for age and genomic estimates of and self-reported race/ethnicity. Variations in four potassium channel genes: (1) potassium voltage-gated channel, delayed rectifier, subfamily S, member 1 (KCNS1); (2) potassium inwardly rectifying channel, subfamily J, member 3 (KCNJ3); (3) KCNJ6; and (4) potassium channel, subfamily K, member 9 (KCNK9) were associated with the occurrence of breast pain. Findings from this study warrant replication in an independent sample of women who report breast pain following one or more breast biopsies.
KEYWORDS: breast cancer; breast pain; candidate genes; potassium channel genes; preoperative pain
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Sent: Wednesday, August 20, 2014 9:39 PM
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Subject: Companion manuscripts JPAIN-D-14-00142R1 and JPAIN-D-14-00143R1:

Dear Dr. Miaskowski:

I am writing in regard to the companion manuscripts you submitted to The Journal of Pain (JPAIN-D-14-00142 - PERSISTENT ARM PAIN IS DISTINCT FROM PERSISTENT BREAST PAIN FOLLOWING BREAST CANCER SURGERY, and JPAIN-D-14-00143R1 - PERSISTENT BREAST PAIN FOLLOWING BREAST CANCER SURGERY IS ASSOCIATED WITH PERSISTENT SENSORY CHANGES, PAIN INTERFERENCE, AND FUNCTIONAL IMPAIRMENTS). As you know, both papers were revised and re-reviewed, and we are prepared to accept them. Each paper has two remaining issues that we need to resolve before we can accept the papers, but hopefully these are fairly minor issues to resolve. Please see below:

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Thank you, and congratulations on the pending acceptance of these companion papers.

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Journal: PAIN
Title: VARIATIONS IN POTASSIUM CHANNEL GENES ARE ASSOCIATED WITH DISTINCT TRAJECTORIES OF PERSISTENT BREAST PAIN FOLLOWING BREAST CANCER SURGERY
ID: PAIN-D-14-12279R2
Format: Research Paper
Authors: Dale J Langford; Steven M Paul; Claudia West; Laura B Dunn; Jon D Levine; Kord M Kober; Marylin J Dodd; Christine Miaskowski, PhD; Bradley E Aouizerat, MAS, PhD

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